PROSTATE CANCER

Effects of tertiary Gleason pattern 5 on oncological outcome

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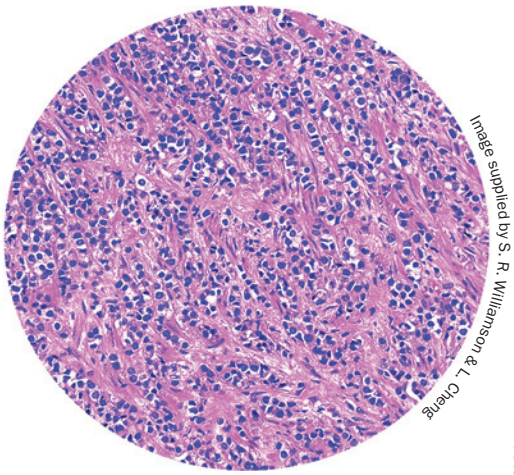
Refers to Lucca, I. *et al.* Validation of tertiary Gleason pattern 5 in Gleason score 7 prostate cancer as an independent predictor of biochemical recurrence and development of a prognostic model. *Urol. Oncol.* http://dx.doi.org/10.1016/j.urolonc.2014.08.011



The prognostic implications of a tertiary component of Gleason pattern 5 cancer at radical prostatectomy remain incompletely understood. A newly published study highlights the relationship between tertiary pattern 5 cancer, other risk factors and clinical outcomes. Authors propose a prognostic model to identify patients with the greatest need for adjuvant therapy.

The Gleason grading system has been recognized for decades as a powerful tool for predicting the outcome of patients with prostate cancer; however, despite its widespread use in clinical practice, uncertainty and debate over its applicability remain in a number of areas.[1] For example, the significance of a minor, higher grade or tertiary Gleason pattern, such as a small component of Gleason pattern 5 in an otherwise Gleason score 7 cancer remains uncertain. In a newly published, large, multicentre study of over 4,000 patients, Lucca and colleagues[2] investigated the implications of tertiary Gleason pattern 5 in radical prostatectomy specimens for the prediction of biochemical recurrence in patients with predominantly Gleason score 7 cancers. The authors used these data to create a prognostic model for optimal clinical management of this heterogeneous group of patients.[2]

> “...Lucca *et al.* provides additional evidence for the prognostic value of a tertiary Gleason pattern 5 component”

In 2005, many updates to the Gleason grading system were formalized, including classification of several morphologic patterns as Gleason pattern 4.[3] As a result of this formalization, incidence of Gleason score 7 cancer has increased in modern practice, and outcomes for these patients are highly variable. Some patients experience an outcome similar to that of Gleason score 3 + 3 = 6, whereas others progress to biochemical recurrence, metastasis and death from prostate cancer. When a minor Gleason pattern of higher grade than that detected in the majority of the tumour is present in prostate needle-biopsy specimens, current guidelines require inclusion of this higher-grade pattern in the Gleason score. Therefore, a tumour with a predominance of Gleason patterns 3 or 4 and minor pattern 5 would be reported as either 3 + 5 = 8 or 4 + 5 = 9, an approach driven largely by the inability of prognostic nomograms and tables to account for a tertiary pattern.[3] However, extrapolating to the entire prostate gland, a substantial number of such patients are likely to have Gleason score 7 cancers with a minor fraction of the tumour composed of Gleason pattern 5 in the gland as a whole. In this setting, the effect of such a tertiary pattern on biochemical recurrence has been the subject of several studies over the past decade.[4–9]

Lucca *et al.*[2] evaluate this challenge in a large, multicentre cohort of 4,146 patients, of whom 416 (10%) were found to have a tertiary Gleason pattern 5. The results suggest the presence of tertiary Gleason pattern 5 is associated with biochemical recurrence in both univariant and multivariant analyses. Standard clinical and pathological variables were adjusted for in the analyses, including preoperative serum PSA level, Gleason score, pathological stage and margin status.[2] The authors propose a risk score for biochemical recurrence in patients with a tertiary Gleason pattern, rather than inherently considering the entire cohort as high-risk patients. The proposed risk stratification tool takes into account serum PSA levels ≥10 (1 point), pathologic stage pT3b (1 point), positive surgical margin (1 point) and primary Gleason pattern 4 (2 points) as adverse features. Under this stratification, patients with a low-risk score (0–1 point) had 5-year biochemical-recurrence-free survival of 76.3%, compared with 18.5% in the high-risk group (3–5 points).[2] The authors hypothesize that, if validated by other studies, this high-risk group might be the most appropriate population for adjuvant clinical trials, whereas for the low-risk and intermediate-risk groups, serial PSA measurements could be employed to monitor long-term risk.[2]

The results of this investigation are largely similar to those found in other studies of the effect of a tertiary Gleason pattern on biochemical recurrence and cancer survival.[4–8] In another concurrent, large study, 2,396 (22.4%) of 11,226 consecutive patients undergoing radical prostatectomy had a tertiary Gleason pattern.[6] In this study, inclusion criteria were less restrictive, as patients with other Gleason scores and lymph node metastases were also included.[6] However, similar findings were reported, in that a tertiary Gleason pattern was found to be an independent predictor of biochemical recurrence in the subgroup of patients with Gleason score 7 tumours. Data from patient groups that were excluded from the study by Lucca and colleagues,[2] (patients with

Gleason score 3 + 3 and a minor tertiary pattern 4 of <5% and patients with Gleason scores ≥8) were also analysed,[6] and in this setting, a tertiary Gleason pattern was not found to be an independent predictor of biochemical recurrence.[6] Although patients who received adjuvant therapy were included in the analysis, statistical analysis excluding these patients yielded similar results.[6]

The combined fraction of high-grade cancer patterns is another parameter that has also been examined for predicting outcome after radical prostatectomy (Gleason patterns 4 and 5 together).[4,10] This combined proportion of high-grade cancer arguably has the greatest effect on prognosis at predominantly the high and low ends of the spectrum. However, one large study analysing this stratification found patients with greater than 20% high-grade cancer patterns to have a 10-year cancer-specific survival of 67%, compared with 85% for those with less than 20% Gleason patterns 4 and 5, and 100% in those without any high-grade component.[10] The importance of the overall fraction of high-grade patterns is also highlighted by the predictive-risk score proposed by Lucca and co-workers,[2] in which a primary Gleason pattern of 4 receives the highest weighting of any single parameter.

As Lucca and colleagues[2] note, although they examine a large cohort of patients, a centralized review of the pathology of study cases was not available to confirm and evaluate the presence and extent of the tertiary Gleason pattern. Pertinently, the authors define a tertiary Gleason pattern as comprising <5% of the entire tumour. No consensus currently exists on such a definition in the radical prostatectomy setting.[1,3] For example, a tumour composed of 60% Gleason pattern 4, 30% Gleason pattern 3 and 10% Gleason pattern 5 at prostatectomy would be regarded by some pathologists as Gleason score 4 + 5 = 9 (using the 5% cutoff), whereas others would regard the pattern 5 component as tertiary, regardless of extent, as long as it is the least prevalent of the three patterns. The latter approach has been used in several other studies evaluating tertiary Gleason patterns, which might at least partly contribute to differences in study populations and outcomes.[6,8,9]

In summary, although the Gleason score is established as a powerful prognostic tool in the management of prostate cancer, debate and uncertainty remain with respect to a number of aspects of its application. The study by Lucca *et al.*[2] provides additional evidence for the prognostic value of a tertiary Gleason pattern 5 component. Application of a novel prognostic model, including the use of a combined percentage of Gleason pattern 4 and 5, might improve the clinical management of patients with prostate cancer, if validated in future studies.

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Competing interests
The authors declare no competing interests.

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